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CANADIAN PATENT

VERIFYING COMPOSITION

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Granted to Chas. Pfizer & Co., Inc., Brooklyn, New York, U.S.A.

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This invention is concerned with orally administered medicaments and more particularly with therapeutic compositions whose consumption by the patient is capable of verification.

The variety of antibacterial and other medicaments suitable for oral administration has multiplied in recent years. It is the particular virtue of such agents that they may be self-administered by the patient, thereby relieving the physician of a considerable burden. This is a great advantage, particularly in underdeveloped areas where the shortage of physicians is acute.

However, the physician who prescribes self-medication cannot be sure that the patient will faithfully follow the regimen. In any group of patients, there are almost invariably some who will fail to adhere to the prescribed schedule. This proportion is undoubtedly greatest where social, cultural or language barriers exist. The problem is particularly serious in the treatment of chronic diseases such as tuberculosis, where failure to take prescribed medication may not be immediately detected, and in the psychotherapeutic area, where the patient's consistent cooperativeness may be in question. As the range of diseases treated on an ambulatory self-medication basis continues to increase, there is a growing need for an accurate method of evaluating the regularity with which a patient takes his

drugs in th absenc of direct supervision.

A method for evaluating the reliability of a given patient in this respect might be based on identification of the drug or its metabolic products in the urine. Unfortunately, however, most drugs are not excreted in forms which can readily be detected with the equipment within the reach of the average hospital laboratory. The detection in the urine of the important tuberculostatic agent, isoniazid, presents typical difficulties.

An inexpensive method which is both safe and reliable has now been discovered for overcoming this problem. According to this discovery, the oral medicament is "tagged" with tracer amounts of riboflavin. When the patient consumes a composition containing the therapeutic agent in combination with an adequate amount of riboflavin, the riboflavin may be readily detected in the urine, thereby verifying consumption of the drug. The patient who is not accepting medication can thus be quickly detected and corrective measures taken.

The oral medicament may be any desired drug, including an antibacterial agent such as an antibiotic or tuberculostatic agent (e.g. isoniazid), or it may be a psychotherapeutic agent (e.g. N-benzyl-beta-isonicotinylhydrazinopropionamide).

For reliable detection in the urine, it is desirable that the riboflavin be administered at a level of at least about 0.5 mg. per kilogram body weight per day. The proportion of riboflavin to be incorporated in the composition with the medicament will be determined by the medicament dosage rate. A therapeutic agent which is administered

at the rate of about 5 mg. per kg. per day will be combined in a proportion of at least about one part by weight of riboflavin to ten parts by weight of medicament, while a drug which is administered at a lower rate will require a correspondingly higher proportion of riboflavin. Daily dosage levels even lower than 0.5 mg. riboflavin per kg. may also be employed, but it becomes difficult to distinguish riboflavin administered at such levels from that normally present in the urine, and reliability is affected. Riboflavin dosage levels of about 0.8-1.6 mg. per kg. per day give excellent results at low cost, and will usually be preferred. Of course, levels up to about 4 mg. per kg., or even higher, may be administered without ill effect, but there is usually no added advantage. It should be understood that instead of riboflavin itself, i.e. Vitamin B_2, an equivalent quantity of the commonly employed salts of its 5'-phosphate ester may be used instead. Thus, for example, riboflavin 5'-phosphate sodium may be employed, and is included within the scope of the term "riboflavin" as employed herein.

The riboflavin content of the urine is readily determined by means of fluorescence measurements with a photofluorometer, employing the standard riboflavin assay technique described in the U.S. Pharmacopeia XV, page 912, December, 1955. It is found that the riboflavin content of urine normally does not exceed 1.5-2.5 mcg. per ml. This level is exceeded, however, in those patients who have consumed the therapeutic compositions of the present invention at the recommended dosage level within the previous 12-8 hr. Where the patient is taking supplementary vitamin

capsules, corresponding to about 3-9 mg. riboflavin per day for example, the normal urine content may rise to about 3.5 mcg. per ml. This should be of course taken into account in interpreting results, but causes no difficulty, since the therapeutic compositions of the present invention lead to urine concentrations well above this level, ranging as high as 100 mcg. per ml. during the 24 hours following administration.

The compositions of the present invention may be administered in the form of capsules, tablets or other conventional oral dosage forms. The riboflavin is inexpensive, palatable and stable, and is readily absorbed following oral administration. A normal constituent of the human body, riboflavin is non-allergenic, and no toxic manifestations have been detected following administration at the levels described. In vitro tests have established that riboflavin does not interfere with the therapeutic activity of such drugs as isoniazid with which it is combined. Thus, the present invention provides highly advantageous compositions whose administration can be readily verified by simple laboratory procedures. Not only is this in the best interest of the patient, but it can also greatly enhance the scientific accuracy of drug evaluation programs.

The following examples are provided for illustrative purposes and should not be interpreted as limiting the invention, the scope of which is indicated by the appended claims.

Example I

Tablets are prepared each containing 50 mg. isonicotinic acid hydrazide together with 5 mg. riboflavin. These

tablets are administered to an ambulatory adult female in a single dose corresponding to 5 mg. per kg. isoniazid (0.5 mg. per kg. riboflavin). Urine specimens are taken periodically during a 24 hour period. The entire experiment is subsequently repeated.

The specimens are each diluted and assayed for riboflavin content by measurement of fluorescence with a Coleman electronic photofluorometer, equipped with Coleman (B-2) 12-222 and (PC-2) 14-212 optical filters, against a standard riboflavin solution. Results obtained are summarized below.

Tablets administered before retiring (12 PM)

Elapsed time	Urine riboflavin conc.
0 hrs.	1.6 mcg./ml.
6.5	35
9	4
20	1.9
23	2.1

Tablets administered before breakfast (6 AM)

Elapsed time	Urine riboflavin conc.
0 hrs.	0.7 mcg./ml.
1.5	16
4.5	17
8	4
14.5	2.8
21	2.0
23	1.9

Example II

The subject of this experiment is a normal ambulatory adult male whose usual riboflavin excretion values are found to range from 0.03 to 0.8 mcg. per ml. urine (avg. 0.26 mcg./ml.), as determined on 10 specimens collected on 8 different days.

Capsules containing 250 mg. riboflavin are administered to this subject once daily at 24 hour intervals on 5 successive days. Urine specimens are taken at 5, 17 and 24

hour intervals after each dose, the 24 hour specimen being taken immediately before administration of the next successive dosage. Specimens are assayed as in Example I, with the following results:

Elapsed time after previous dose	Urine Riboflavin Conc., mcg./ml.
0 hrs. (250 mg. admin.)	0.1
5	>15
17	4.5
24 (250 mg. admin.)	4.3
5	>15
17	14.8
24 (250 mg. admin.)	3.3
5	>15
17	14.8
24 (250 mg. admin.)	3.4
5	>15
17	15
24 (250 mg. admin.)	5.1
5	>15
24	5.0
48	2.3
72	1.3
96	0.1

Example III

Tablets containing 50 mg. isoniazid together with 8 mg. riboflavin are administered to a normal ambulatory adult female at 24 hour intervals on 3 successive days. On each day the tablets are administered at the rate of 5 mg. isoniazid per kg. body weight (0.8 mg./kg. riboflavin) in a single dose just before retiring. Urine specimens are taken periodically and assayed as before, with the results given below.

Elapsed time after previous dose	Urine Riboflavin Conc., mcg./ml.
0 hrs. (0.8 mg./kg. admin.)	2.0
24	2.7
8	>6
12	>6
16	>6
20	5.8
24 (0.8 mg./kg. admin.)	5.6
8	>6
12	>6
16	>6
20	4.0
24	4.1
48	2.7

Example IV

Riboflavin excretion is determined over a 9-day period in two female hospital patients on regular hospital diets. Spot urine specimens are taken daily at 8 AM and 8 PM, and in addition the total 24 hr. sample is collected for each 8 AM to 8 AM period. Specimens are assayed as previously described. Between 7 and 8 AM of the second 24-hour period one 3 mg. riboflavin capsule is administered to Patient No. 1, and 2 capsules to Patient No. 2. These correspond to 0.07 and 0.1 mg. B_2/kg. respectively. Between 7 and 8 AM of the seventh 24-hour period Patient No. 1 is administered 8 tablets each containing 50 mg. isoniazid plus 8 mg. riboflavin (corresponding to 10 mg./kg. isoniazid plus 1.6 mg./kg. B_2). At the same time Patient No. 2 is administered 6 such tablets (corresponding to 5 mg./kg. isoniazid plus 0.8 mg./kg. B_2). Results are given in the following table.

	Patient No. 1		Patient No. 2	
Day	24-hour B_2 excretion, mg.	B_2 Conc. mcg./ml.	24-hour B_2 excretion, mg.	B_2 Conc. mcg./ml.
1	1.8	8AM 2.0 8PM 0.9	1.3	8AM 2.3 8PM 1.1
2	1.6	8AM 1.6 8PM 0.9	1.1	8AM 1.4 8PM 1.3
	(0.07 mg B_2/kg admin. 7-8AM)		(0.1 mg B_2/kg admin. 7-8AM)	
3	2.8	8AM 3.0 8PM 5.8	5.6	8AM 1.1 8PM 5.0
4	1.9	8AM 2.5 8PM 0.6	1.1	8AM 1.8 8PM 0.9
5	*	8AM 1.1 8PM 0.5	*	8AM 0.9 8PM 0.6
6	1.0	8AM 2.5 8PM 0.5	*	8AM 0.4 8PM 1.6
7	0.8	8AM 2.5 8PM 0.7	0.7	8AM 1.3 8PM 0.3
	(1.6 mg B_2/kg admin. 7-8AM)		(0.8 mg B_2/kg admin. 7-8AM)	
8	6.7	8AM 2.6 8PM 6.0	14.7	8AM 1.0 8PM 9.9
9	1.0	8AM 3.6 8PM 1.1	*	8AM 1.8 8PM 1.6
		8AM 0.8		8AM 1.7

* Specimen incomplete

Example V

Urine specimens are taken 3 times daily from a group of 7 male and 3 female ward patients for a period of 8 days. Vitamin capsules totalling 3-9 mg. B_2 per patient are administered on the second and third days. Tablets containing 50 mg. isoniazid plus 8 mg. B_2 are administered on the fourth, fifth and sixth days, at the rate 0.8 mg. B_2/kg. body weight per day. All medication is furnished under direct supervision between 7 and 8 AM. Specimens are assayed as previously described, to determine the relative effect of conventional vitamin supplementation and the isoniazid-riboflavin composition on urine riboflavin content.

Riboflavin Determinations on Ten Subjects' Urine Specimens

Day	Highest Value Found		Number of Specimens Assaying: <2.5 mcg./ml.	2.5-3.5 mcg/ml	>3.5 mcg/ml
1	6 mcg./ml.	7-8 AM	10	0	0
		12-1 PM	7	2	1
		7-8 PM	10	0	0
2*	13 mcg./ml.	7-8 AM	7	3	0
		12-1 PM	6	4	0
		7-8 PM	3	4	3
3*	6 mcg./ml.	7-8 AM	4	5	1
		12-1 PM	5	3	2
		7-8 PM	5	4	1
4**	75 mcg./ml.	7-8 AM	7	3	0
		12-1 PM	0	0	10
		7-8 PM	0	0	10
5**	105 mcg./ml.	7-8 AM	1	3	6
		12-1 PM	0	1	9
		7-8 PM	0	0	10
6**	69 mcg./ml.	7-8 AM	1	5	4
		12-1 PM	0	0	10
		7-8 PM	0	0	10
7	13 mcg./ml.	7-8 AM	0	4	6
		12-1 PM	3	1	6
		7-8 PM	2	5	3
8	6 mcg./ml.	7-8 AM	2	8	0
		12-1 PM	3	6	1
		7-8 PM	2	7	1

* 3-9 mg. B_2 administered at 7-8 AM

** 0.8 mg. B_2/kg. + isoniazid administered at 7-8 AM

Example VI

A group of unsupervised outpatients is placed on a prescribed schedule of 5 mg./kg. isoniazid daily in the form of 50 mg. tablets each "tagged" with 8 mg. riboflavin (equivalent to 0.8 mg. B_2/kg. daily). Urine specimens are collected on unscheduled home or routine clinic visits, over periods of two to 6 months. Assay results are given below for a typical cooperative patient, and for a typical patient whose ability to follow a home-treatment regimen is open to serious question. Specimens are collected at varying times of day.

	B_2 Urine Concentration, mcg./ml.	
Specimen No.	Patient No. 1	Patient No. 2
1 (before commencing medication)	<2.5	<2.5
2	15	"
3	40	"
4	15	5
5	36	<2.5
6	8	"
7	27	"
8	25	"
9	12	30
10	10	<2.5
11	25	28
12	6	35
13	6	4
14 (after discontinuing medication)	<2.5	<2.5

Example VII

A tablet base is prepared by blending the following ingredients in the indicated proportions by weight:

Sucrose USP	80.3
Tapioca starch	13.2
Magnesium stearate	6.5

Into this base is blended sufficient N-benzyl-beta-isonicotinylhydrazinopropionamide (U.S.Patent 2,894,973)

and riboflavin to provide tablets each containing 25 mg. of the psychotherapeutic agent and 10 mg. of the riboflavin. Prescribed to adults at the rate of about 6 tablets daily, these tablets provide a suitable riboflavin urine level to verify compliance with the prescribed regimen.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A therapeutic composition comprising an orally administrable medicament in combination with sufficient riboflavin to provide a daily tracer dosage of at least about 0.5 mg. riboflavin per kilogram body weight of the consumer of said composition.

2. The composition of claim 1 wherein said medicament is an antibacterial agent.

3. The composition of claim 1 wherein said medicament is a tuberculostatic agent.

4. The composition of claim 1 wherein said medicament is a psychotherapeutic agent.

5. A therapeutic composition comprising about 50 parts by weight of isoniazid in combination with about 8 parts by weight of riboflavin.